SECTION 1. INTRODUCTION, OVERVIEW, AND CONCLUSIONS

Introduction

Organization and Development of the 1983 Report

The content of the Report is the work of numerous scientists and experts within the Department of Health and Human Services as well as from outside the organization. Individual manuscripts were written by experts nationally and internationally recognized for their scientific contributions to the understanding of cardiovascular diseases. These manuscripts were reviewed individually by other experts, within and outside the U.S. Public Health Service, and the entire Report was reviewed by a broad-based panel of distinguished cardiovascular scientists. The 1983 Report includes a Foreword by the Assistant Secretary for Health of the Department of Health and Human Services and a Preface by the Surgeon General of the U.S. Public Health Service. The body of the report consists of eight sections and two appendices, as follows:

- Section 1. Introduction, Overview, and Conclusions
- Section 2. Arteriosclerosis
- Section 3. Coronary Heart Disease
- Section 4. Cerebrovascular Disease
- Section 5. Atherosclerotic Peripheral Vascular Disease and Aortic Aneurysm
- Section 6. Pharmacological and Toxicological Implications of Smoke Constituents on Cardiovascular Disease
- Section 7. Changes in Cigarette Smoking Behavior in Clinical and Community Trials
- Section 8. The Effect of Cigarette Smoking Cessation on Coronary Heart Disease
- Appendix A. Trends in Cardiovascular Diseases
- Appendix B. Trends in U.S. Cigarette Use, 1965 to 1980

Historical Perspective

Early reports linking smoking with a greater risk of developing cardiovascular disease occurred around the turn of the century. An early series of studies, initiated in 1904 by Erb, found a much higher percentage of smokers than of nonsmokers with intermittent claudication; only 10 percent of his patients with claudication were nonusers of tobacco. As early as 1934, Howard made the observation that the increasing prevalence of coronary heart disease noted since the first World War might be a result of the greatly increased use of cigarettes.

By the turn of the century, numerous studies had demonstrated clinically and experimentally that cigarette smoking or cigarette smoke constituents, most notably nicotine, caused an elevation in blood pressure and heart rate during smoking.

The first major prospective study results were made public in 1954 in the United States by Hammond and Horn and found a strong association between cigarette use among men and coronary heart disease (CHD). Overall, smokers were found to carry a 70 percent greater risk of dying from CHD than nonsmokers; heavy smokers had CHD mortality rates almost two and one-half times greater than nonsmokers. Hammond and Horn also noted a consistent dose–response relationship with the number of cigarettes consumed per day.

In the intervening 30 years, numerous additional epidemiological mortality studies were undertaken to examine this issue. These included studies in the United Kingdom, Canada, Sweden, Japan, and Switzerland in addition to the United States. In total, they represent more than 20 million person-years of observation. Findings from these studies have been remarkably uniform: smokers have much higher death rates from coronary heart disease than do nonsmokers, despite the fact that these studies were conducted in varying populations, were geographically diverse, and involved differing methodologies.

The first major U.S. Public Health Service review of the relationship between smoking and heart disease was conducted by the Surgeon General's Advisory Committee on Smoking and Health in 1964. Although the Committee noted that male smokers had higher death rates from coronary heart disease, it was unable to conclude that the association had causal significance. However, it was noted in the report that "the causative role of these factors [risk factors including cigarette smoking] in coronary disease, though not proven, is suspected strongly enough to be a major reason for taking countermeasures against them. It is also more prudent to assume that the established association between cigarette smoking and coronary disease has causative meaning than to suspend judgement until no uncertainty remains."

Since the release of the original Report of the Surgeon General in 1964, additional studies dealing with cigarette smoking and CHD have been summarized in the series of annual reports of the Surgeon General *The Health Consequences of Smoking*. By 1979, the magnitude of the epidemiological, pathological, clinical, and experimental evidence had grown to the point that the Surgeon General's Report concluded: "Smoking is causally related to coronary heart disease in the common sense of that idea and for the purposes of preventive medicine."

Overview

In 1980, diseases of the circulatory system were responsible for approximately one-half of the total U.S. mortality. *CHD was the*

single most important cause of death, accounting for approximately 30 percent of all U.S. deaths.

Cigarette smoking is one of the three major independent CHD risk factors. The magnitude of the risk associated with cigarette smoking is similar to that associated with the other two major CHD risk factors, hypertension and hypercholesterolemia; however, because cigarette smoking is present in a larger percentage of the U.S. population than either hypertension or hypercholesterolemia, cigarette smoking ranks as the largest preventable cause of CHD in the United States. Cigarette smoking also acts synergistically with the other major risk factors to greatly increase the risk for CHD.

Arteriosclerosis is the predominant underlying cause of cardiovascular disease, and atherosclerosis is the form of arteriosclerosis that most frequently causes clinically significant disease, including CHD, atherothrombotic brain infarction, atherosclerotic aortic disease, and atherosclerotic peripheral vascular disease. Cigarette smoking contributes both to the development of atherosclerotic lesions and to the clinical manifestations of atherosclerotic vascular disease, including sudden death. Although the precise pathophysiologic basis of these clinical manifestations is not understood, it may be related to several deleterious cardiovascular effects of cigarette smoking, including production of an imbalance between myocardial oxygen supply and demand, a decrease in the threshold for ventricular fibrillation, and an increase in platelet aggregation. Nicotine and carbon monoxide are the tobacco smoke constituents most closely associated with these adverse effects; other cigarette smoke constituents such as hydrogen cyanide, oxides of nitrogen, and carbon disulfide are being studied for possible pathogenic cardiovascular effects.

Cigarette smoking is the most important risk factor for atherosclerotic peripheral vascular disease, which usually involves the lower extremities. Smoking cessation is probably the single most important intervention in the management of this disorder. The effect of cigarette smoking to aggravate and accelerate the development of atherosclerosis is more striking in the aorta than in any other vessels. Cigarette smoking is associated with an increased risk for cerebrovascular disease, especially in younger age groups, but this effect is less marked than for atherosclerotic disease at other sites. Women cigarette smokers experience an increased risk for subarachnoid hemorrhage; the use of both cigarettes and oral contraceptives greatly increases this risk.

Smoking cessation is associated with decreased mortality and morbidity from atherosclerotic vascular disease. Prospective epidemiologic studies have shown that former cigarette smokers reduce their CHD death risk from that of current smokers to that of nonsmokers over approximately a 15-year period after stopping

smoking. The beneficial effects of quitting are not explained by differences in baseline characteristics between quitters and continuing smokers. CHD intervention trials have successfully demonstrated the feasibility of reducing cigarette consumption; these trials also documented a significant reduction in CHD mortality.

Conclusions of the 1983 Report

The purpose of this Report is to review in depth the many sources of scientific evidence relating cigarette smoking to individual cardiovascular disease entities. Listed below are the major findings of this review.

Arteriosclerosis

1. A preponderance of evidence both from prospective studies with autopsy followup and from autopsy studies with retrospective smoking data indicates that cigarette smoking has a significant positive association with atherosclerosis. This evidence suggests that cigarette smoking has the effect of aggravating and accelerating the development of atherosclerotic lesions in the artery wall and that its effect is not limited to those events related to the occlusive episode. The effects are most striking for aortic atherosclerosis; a significant positive relationship also exists between cigarette smoking and atherosclerotic lesions in the coronary arteries, at least for most high risk populations. Cigarette smoking could also be associated with other factors that precipitate thrombosis, hemorrhage, or vasoconstriction leading to occlusion and ischemia.
2. Some evidence exists that cigarette smoke alters total serum cholesterol concentrations and lipoprotein composition in ways that would be expected to increase the development of atherosclerosis. Recent studies of the effects of smoking on the hemostatic system indicate effects on platelet function.
3. Although the specific mechanisms by which tobacco smoke affects arteriosclerosis have not been clearly delineated, the effects of cigarette smoking on the atherosclerotic lesions that underlie cardiovascular disease seem well established.

Coronary Heart Disease

1. Cigarette smoking is a major cause of coronary heart disease in the United States for both men and women. Because of the number of persons in the population who smoke and the increased risk that cigarette smoking represents, it should be considered the most important of the known modifiable risk factors for CHD.

2. Overall, cigarette smokers experience a 70 percent greater CHD death rate than do nonsmokers. Heavy smokers, those who consume two or more packs per day, have CHD death rates between two and three times greater than nonsmokers.
3. The risk of developing CHD increases with increasing exposure to cigarette smoke, as measured by the number of cigarettes smoked daily, the total number of years one has smoked, and the degree of inhalation, and with an early age of initiation.
4. Cigarette smokers have a twofold greater incidence of CHD than do nonsmokers, and heavy smokers have an almost fourfold greater incidence.
5. Cigarette smoking is a major independent risk factor for CHD, and it acts synergistically with other risk factors (most notably, elevated serum cholesterol and hypertension) to greatly increase the risk of CHD.
6. Women have lower rates for CHD than do men. In particular, CHD rates for women are lower prior to the menopause. A part of this difference is due to the lower prevalence of smoking in women, and for those women who do smoke, to the tendency to smoke fewer cigarettes per day and to inhale less deeply. Among those women who have smoking patterns comparable to male smoking patterns, the increments in CHD death rates are similar for the two sexes.
7. Women who use oral contraceptives and who smoke increase their risk of a myocardial infarction by an approximately tenfold factor, compared with women who neither use oral contraceptives nor smoke.
8. Cigarette smoking has been found to significantly elevate the risk of sudden death. Overall, smokers experience a two to four times greater risk of sudden death than nonsmokers. The risk appears to increase with increasing dosage as measured by the number of cigarettes smoked per day and diminishes with cessation of smoking.
9. The CHD mortality ratio for smokers compared with nonsmokers is greater for the younger age groups than for the older age groups. Although the smoker-to-nonsmoker mortality ratio narrows with increasing age, smokers continue to experience greater CHD death rates at all ages.
10. Cigarette smoking has been estimated to be responsible for up to 30 percent of all CHD deaths in the United States each year. During the period 1965 to 1980 there were over 3 million premature deaths from heart disease among Americans attributed to cigarette smoking. Unless smoking habits of the American population change, perhaps 10 percent of all persons now alive may die prematurely of heart disease attributable to

their smoking behavior. The total number of such premature deaths may exceed 24 million.

11. Cessation of smoking results in a substantial reduction in CHD death rates compared with those of persons who continue to smoke. Mortality from CHD declines rapidly after cessation. Approximately 10 years following cessation the CHD death rate for those ex-smokers who consumed less than a pack of cigarettes daily is virtually identical to that of lifelong nonsmokers. For ex-smokers who had smoked more than one pack per day, the residual risk of CHD mortality is proportional to the total lifetime exposure to cigarette smoke.
12. Epidemiologic evidence concerning reduced tar and nicotine or filter cigarettes and their effect on CHD rates is conflicting. No scientific evidence is available concerning the impact on CHD death rates of cigarettes with very low levels of tar and nicotine.
13. Smokers who have used only pipes or cigars do not appear to experience substantially greater CHD risks than nonsmokers.

Cerebrovascular Disease

1. Data from numerous prospective mortality studies have shown an association between cigarette smoking and cerebrovascular disease. This risk is most evident in the younger age groups, and the effect diminishes with increasing age, with little or no effect noted after age 65. No consistent dose–response effect has been demonstrated.
2. Women cigarette smokers experience an increased risk for subarachnoid hemorrhage. However, the use of both cigarettes and oral contraceptives greatly increases the risk for subarachnoid hemorrhage among women.

Atherosclerotic Peripheral Vascular Disease and Aortic Aneurysm

1. Cigarette smoking is the most powerful risk factor predisposing to atherosclerotic peripheral arterial disease.
2. Smoking cessation plays an important role in the medical and surgical management of atherosclerotic peripheral vascular disease.
3. Death from rupture of an atherosclerotic abdominal aneurysm is more common in cigarette smokers than in nonsmokers.

Pharmacological and Toxicological Implications of Smoke Constituents on Cardiovascular Disease

1. Over 4,000 different compounds have been identified in tobacco smoke.

2. Nicotine exerts an effect on ganglionic cells, producing transient excitation. The pharmacological effects are small, but are reinforced several times daily in habitual smokers. The exact mechanisms whereby nicotine might influence cardiovascular events are unknown, but a lowering of the ventricular fibrillation threshold is dose related to nicotine levels.
3. Carbon monoxide may act to precipitate cardiac symptomatology or ischemic episodes in individuals already compromised by coronary disease. In addition, carbon monoxide binds to hemoproteins, potentially inhibiting their functions.
4. Several studies have shown that smokers may alter their smoking behavior when they switch to low-yield cigarettes. This compensatory behavior may lead to the increased uptake of gas phase constituents including carbon monoxide, hydrogen cyanide, and nitrous oxides.
5. It is unlikely that a "safe cigarette" can be developed that will reduce cardiovascular risk.

Changes in Cigarette Smoking Behavior in Clinical and Community Trials

1. Smokers involved in intervention programs demonstrate higher smoking cessation rates than those in control groups.
2. In general, the success of smoking intervention programs is related to the amount of intervention provided.

The Effect of Cigarette Smoking Cessation on Coronary Heart Disease

1. In the four intervention trials involving mortality followup of individual men for 5 to 10 years, the intervention groups had a combined total of 10 percent fewer CHD deaths than did the comparable control groups. Differences for other causes of death or for total deaths were not significant.
2. In these trials, the amount of cigarette smoking has been reduced 10 to 50 percent more in the intervention group than in the control group, demonstrating that intervention can alter smoking behavior.
3. In the two trials involving morbidity followup, the intervention groups had 4 and 45 percent lower total CHD incidence than did the respective control groups.
4. The relative reductions in CHD mortality in each of the four intervention studies involving individual followup are reasonably consistent with the reduction in CHD risk factors, and for a combination of all four studies, the reduction is statistically significant.

5. Numerous studies have shown that those who quit cigarette smoking experience a substantial decrease in CHD mortality and an improvement in life expectancy.
6. A number of prospective epidemiological studies indicate that former cigarette smokers substantially reduce their CHD and total death rates from that of current smokers.

Trends in Cardiovascular Diseases

The evidence supports the conclusion that changes in smoking habits have contributed to substantial improvement in mortality rates from the cardiovascular diseases in the United States.

Trends in U.S. Cigarette Use, 1965–1980

1. The proportion of current regular smokers declined steadily between 1965 and 1980. The decline was steeper among males (from 52.1 to 37.9 percent) than among females (from 34.2 to 29.8 percent).
2. The proportion of never smokers increased steadily from 1965 to 1980 among males (27.6 to 31.6 percent), except those 45 years old and older. Among females, only 20- to 34-year-olds showed an increase in proportion of never smokers.
3. The mean number of cigarettes smoked per day by current smokers increased slightly from 1970 to 1980 (from 20 to 21.7 cigarettes).
4. Males smoked a higher mean number of cigarettes throughout the 1970–1980 period, but the number for males and females increased about the same amount.
5. Heaviest daily consumption was in the middle-aged group (35–65 years). The greatest mean increase was observed among women aged 35 to 44.
6. The proportion of current smokers who smoked less than 20 cigarettes per day decreased between 1970 and 1980 (39.8 to 33.8 percent); the proportion smoking one pack exactly (20 cigarettes) remained constant (34.9 to 34.8 percent); the proportion smoking from 21 to 39 cigarettes increased slightly (13.7 to 14.5 percent); and the proportion smoking two or more packs per day increased from 11.4 to 16.8 percent.
7. The proportion of current smokers who attempted to quit three or more times decreased slightly from 1966 to 1980 (41.2 to 38.7 percent).
8. The proportion of former smokers having made three or more attempts to quit increased sharply (36 to 53.2 percent) from 1966 to 1975.
9. The proportion of current smokers who had attempted to quit during the past year increased from 1966 to 1980 (26.0 to 36.7 percent).

10. Among current smokers, younger persons and females were more likely than older persons and males to have attempted to quit during the previous 12 months.
11. The proportion of former smokers who had attempted to quit during the previous 12 months decreased from 1966 to 1975 (13.8 to 9.8 percent).
12. Among former smokers, younger persons and females were more likely than older persons and males to have quit during the previous 12 months.

SECTION 2. ARTERIOSCLEROSIS

Introduction and Definition of Terms

Arteriosclerosis is the predominant underlying cause of cardiovascular diseases, including coronary heart disease (CHD), cerebral infarction, arteriosclerotic peripheral vascular disease, and atherosclerotic aortic aneurysm. The specific relationships of tobacco use and these conditions, as well as an overview of known and suspected risk factors for cardiovascular disease, are reviewed in other sections.

Because arteriosclerosis is sometimes used in a broad sense to cover a variety of arterial lesions, the nomenclature and terminology used in this section will be defined.

Arteriosclerosis is a generic term that includes practically any arterial disease that leads to thickening and hardening of arteries of any size.

Atherosclerosis is a specific form of arteriosclerosis. Its most distinctive feature is the accumulation of lipid in the intima of large elastic arteries (aorta) and medium-sized muscular arteries (coronary, femoral, carotid, and others). In addition to lipid, cells, connective tissue fibers, and various blood components accumulate in the lesions. A number of complications, including thrombosis, hemorrhage into a plaque, and ulceration, can also occur in or upon the lesions. The hallmarks of atherosclerosis are its intimal location during the initial stage, the involvement of large- and medium-sized arteries, and the accumulation of fat in the lesion. Atherosclerosis is the form of arteriosclerosis that most frequently causes clinically significant disease.

Mönckeberg's medial calcific sclerosis, characterized by calcification of the medial layer of muscular arteries, and *arteriolosclerosis,* characterized by thickening, fibrosis, hyalinization, and narrowing of arterioles, are other types of arteriosclerosis quite distinct from atherosclerosis. They are beyond the scope of this section. Medial and arteriolar lesions have sometimes caused confusion in interpreting experimental studies, principally those in which rabbits and rats have been used. Only the intimal lesions that contain lipid and connective tissue elements in large elastic and medium-sized muscular arteries are models of human atherosclerosis.

The term *atheroma* has been used in several different ways, sometimes to refer to the entire process of atherosclerosis and sometimes to describe a specific lesion. Some pathologists use the word to mean a large atherosclerotic plaque containing a pool of necrotic cells, lipid, and connective tissue. Atheroma has also been used to refer to any lesion of atherosclerosis, including fatty streaks, fibrous plaques, or complicated or calcified lesions.

The following working definitions are offered for different types of atherosclerotic lesions detectable grossly after staining vessels with Sudan IV or other fat stains.

A *fatty streak* is a fatty intimal lesion that is stained distinctly by Sudan IV and shows no other underlying change. Fatty streaks are flat or only slightly elevated in opened fresh or immersion fixed vessels. They do not significantly narrow the lumina of blood vessels.

A *fibrous plaque* is a firm, elevated intimal lesion that in the fresh state is usually gray-white, glistening, and translucent. Human fibrous plaques characteristically contain fat. A thick fibrous connective tissue cap containing varying amounts of lipid covers a more concentrated "core" of lipid. If a lesion also contains hemorrhage, thrombosis, ulceration, or calcification, that lesion is classified according to one of the next two categories.

A *complicated lesion* is an intimal plaque in which there is hemorrhage, ulceration, or thrombosis with or without calcification.

A *calcified lesion* is an intimal plaque in which insoluble mineral salts of calcium are visible or palpable without overlying hemorrhage, ulceration, or thrombosis.

The term *raised atherosclerotic lesion* is sometimes used as a measure of atherosclerosis to include the sum of fibrous plaques, complicated lesions, and calcified lesions. Raised lesions are contrasted with fatty streaks, which typically show little or no elevation above the surrounding intimal surface.

Although this classification scheme implies a pathogenetic sequence, it can be used for descriptive purposes regardless of the theoretical pathogenetic interrelationships among the lesions.

Certain other intimal lesions are sometimes considered as subtypes of atherosclerosis or as lesions predisposing to atherosclerosis. These include musculoelastic or fibromuscular intimal thickening, gelatinous or edematous lesions, and organizing mural thrombi on an otherwise normal intima. The pathogenetic relationship of atherosclerosis and its clinical manifestations is less well established for these lesions, and quantitative information related to the natural history, topography, and geographic pathology is not available. "Rhythmic" or periodic wrinkling of the intimal surface of the aortas of children and adolescents is another change whose relationship to atherosclerosis has not been established.

Clinical Significance of Atherosclerosis

Atherosclerosis is the underlying cause of coronary heart disease (coronary occlusion, coronary thrombosis, myocardial infarction, and angina pectoris) and of one major type of stroke (cerebral thrombosis with infarction). Atherosclerosis also causes aortic aneurysms by weakening the aortic media via encroachment from primarily intimal lesions. Atherosclerosis also sets the stage for arteriosclerotic peripheral vascular disease by occlusive-thrombotic disease of the

distal aorta and by atherosclerotic lesions in the iliac-femoral vessels.

Previous Literature Reviews

The history of our knowledge about atherosclerosis was reviewed by Long (*39*). The morphology and pathogenesis of human atherosclerotic lesions were reviewed in detail by Duff and McMillan (*20*), and the gross and microscopic features of typical coronary and aortic human lesions at various ages were illustrated by McGill et al. (*44*). Data on the worldwide distribution of atherosclerotic lesions among different human populations were published in 1968 (*41*). Strong et al. (*72, 73*) reviewed the development of atherosclerosis by age, sex, and race, by the geographic variation in prevalence and extent of atherosclerosis, and by the relationship of atherosclerotic lesions to risk factors for coronary heart disease. A monograph on arterial smooth muscle cells by Geer and Haust (*22*) contains an extensive review of publications on the nature of cells in atherosclerotic lesions, descriptions of the histologic and ultrastructural features of arterial lesions, and electron micrographs illustrating atherosclerotic lesions. The published proceedings of international symposia on atherosclerosis (*25, 34, 63, 64, 65, 86*) contain review articles and reports of investigative work in atherosclerosis.

Natural History and Topography

Atherosclerosis begins in childhood, but does not usually become clinically manifest through its ischemic complications until later in life. The simple fatty streak is considered to represent the earliest lesion of atherosclerosis that can be easily recognized either grossly or histologically. The fatty streak is gradually converted into a fibrous plaque in which there is abundant connective tissue as well as lipid. These more advanced intimal lesions with increased amounts of mesenchymal tissue may enlarge to cause progressive stenosis of the vascular lumen. These lesions may undergo sufficient enlargement by accumulated lipid and connective tissue or superimposed mural thrombus to further narrow the lumen, or the lesions may become vascularized and undergo intramural hemorrhage or may become ulcerated and covered by thrombus. In these last instances, rapid occlusion of the artery may result. Under certain circumstances and in certain arterial segments, the lesion may so weaken the underlying media that an aneurysm is produced, or the lesion may become calcified—a change that may represent a healing process, but nevertheless reflects an advanced stage of the atherosclerotic process.

The strong association between cigarette smoking and the clinical manifestations of atherosclerosis is examined in other sections of this Report. This section examines the relationship between cigarette smoking and the development of atherosclerotic lesions and other stages of occlusive arterial disease.

A brief description of the topographic distribution of atherosclerosis in different arterial segments provides additional background information for this section. The topographic distribution of atherosclerotic lesions was reviewed by Duff and McMillan (*20*) and by Glagov and Ozoa (*23*). Schwartz and Mitchell (*68*) described selective involvement of some arteries and areas of localization of arterial plaques in their necropsy survey. Those studies were generally consistent, finding that lesions occur earliest and most extensively in the aorta. Pathologically demonstrable lesions usually develop later and less extensively in the coronary and cerebral arteries; the renal, mesenteric, and pulmonary arteries are the least susceptible to atherosclerotic lesions. A diagrammatic representation of the usual localization of arterial involvement by atherosclerosis is depicted in Figure 1, taken from the National Heart and Lung Institute (NHLI) task force report on arteriosclerosis (*79*).

Studies in the International Atherosclerosis Project (IAP) led to the following conclusions concerning atherosclerosis in the aorta and in the coronary, carotid, vertebral, and intracranial arteries (*43*). The severity of atherosclerosis in one artery does not predict the severity in another artery for an individual case. On a cross-cultural basis, however, the average predilection of a population to raised lesions in one artery is correlated with the predilection in other arteries. The rank order of location–race groups in the IAP is approximately the same regardless of whether the ranking is based on raised lesions in the coronary arteries, the thoracic aorta, the abdominal aorta, or the cerebral arteries. This finding is consistent with the hypothesis that environmental conditions predominantly determine the severity of atherosclerosis in a population, despite large differences in susceptibility to lesions among individuals or among different anatomic loci within the arteries of each person.

In general, the development of atherosclerosis follows a definite sequence. The aorta is involved first, beginning in infancy with fatty streaks that increase rapidly during puberty; fibrous plaques begin in the aorta in the third decade. Fatty streaks begin in the coronary arteries during puberty. They begin to increase significantly and become converted into fibrous plaques in the third decade of life in high risk populations. The carotid arteries begin to be involved with fatty streaks at approximately the same age as does the aorta. The other cerebral arteries begin to be involved at approximately the same age as do the coronary arteries. Raised lesions develop in the

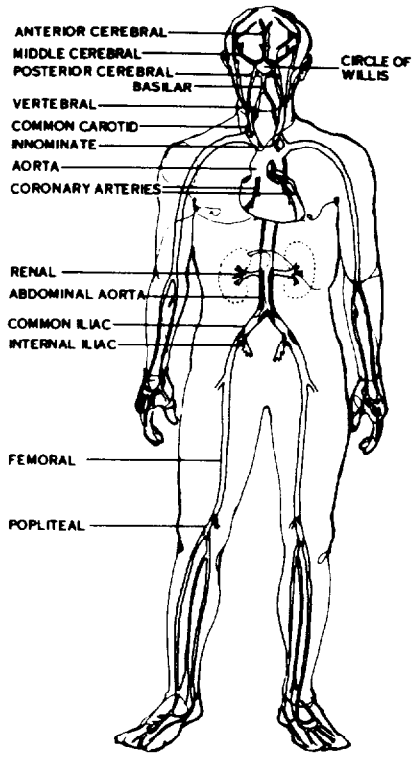

FIGURE 1.—Common sites of atherosclerotic lesions
SOURCE: U.S. Public Health Service (79).

carotid arteries at roughly the same age as in the aorta, but do not develop in the vertebral and intracranial arteries until much later.

Hypotheses of Atherogenesis

A succinct review of the major hypotheses concerning the atherosclerotic process (*47*) summarized various theories of atherogenesis with emphasis on the two major hypotheses—the lipid hypothesis, and the hypothesis that regards atherogenesis as a process involving the conversion of arterial mural thrombi into atherosclerotic plaques.

The lipid hypothesis is based on the frequent occurrence of excessive amounts of cholesterol and lipid in lesions, the positive association between elevated serum lipids and atherogenesis in man and in animals, the association of dietary saturated fats and cholesterol with atherogenesis in man and in experimental animals,

and the association between specific diseases and genetic disorders that affect lipid metabolism and atherogenesis.

The hypothesis concerning the conversion of mural thrombi into atherosclerotic plaques through tissue organization of the mural thrombi (the Duguid-Rokitansky concept) is based largely on pathological observations in man that show morphological evidence compatible with this view of atherogenesis. Such evidence is most convincing in relation to the middle or late development of plaques rather than to their early stages. Many investigators of atherosclerosis have accepted this theory as a basis for plaque progression or complication rather than as a theory of plaque initiation. The demonstration that platelets are capable of interacting with intimal smooth muscle cells to stimulate them to proliferate has now extended this theory to encompass the *initiation* of atherogenesis without necessarily invoking the classical sequence of thrombosis (*59*).

McMillan (*47*) pointed out that there has been a tendency for the proponents of one or the other of these theories to emphasize the rather exclusive importance of one hypothesis when considering various factors that are thought to be of particular importance for atherogenesis (such as cigarette smoking, hypertension, diabetes mellitus, or hyperlipoproteinemia). That is, the atherogenic factors often have been relegated to one or the other theory as independent factors that promote either lipid or thrombotic atherogenesis. Nevertheless, as McMillan (*47*) indicates, the two major theories are not mutually exclusive, but may complement one another in the initiation and progression of atherogenesis.

There is much support for the view that atherosclerosis is best accounted for by the known facts if it is regarded as a multifactorial disease and, in the words of McMillan, "polyetiologic and polypathogenetic."

The finding that some individual fibrous plaques are uniform for one or other of the sex-linked isoenzymes of 6-GPD (*12, 13, 14*) suggests that each mature plaque derives from a single cell and is the basis for a new theory of atherogenesis, the monoclonal hypothesis. This theory suggests that plaques may result from the transformation, genetic or otherwise, of individual cells of the vessel wall into a cell that will react to stimulation and form a plaque. Other observations that fatty streaks are not monotypic (*55*) and that thin plaques tend to be heterotypic, while thicker ones from the same aorta tend to be monotypic (*76*), suggest that the phenomenon of cell adaptation and selection rather than that of transformation may be the basis for plaque monotypism.

The arterial endothelium obviously has a key role in both the lipid and the thrombotic theories. In the lipid theory, the lipoprotein molecules traverse the endothelium in some fashion prior to being

accumulated in a plaque. The thrombotic theory also includes endothelial participation as an essential phenomenon. Endothelial damage or loss may be manifest either as increased permeability to macromolecules or as a focus for platelet adhesion, aggregation, and release; thus, these changes may be atherogenic stimuli. Exposure of the intima to lipoproteins and platelets may be mitogenic for smooth muscle cells, and can affect the arterial lesion by modulating the cellular production of collagen and glycosaminoglycans. This sequence of events indicates how the lipid and thrombotic theories can interrelate in early atherogenesis.

The most popular hypothesis to account for the accumulation of lipid in plaques involves the introduction of excessive amounts of plasma lipoproteins through the endothelial barrier to the intima. The lipoproteins, particularly low density lipoproteins (LDL), are internalized by smooth muscle and other connective tissue cells and are not metabolized rapidly; therefore, the lipid components accumulate in the cells. The sterols that are liberated in the cell lysosomes of arterial cells may become so excessive that high density lipoproteins (HDL) are unable to remove them from the cells and from the intima. With progressive cellular lipid accumulation, cellular necrosis may occur, causing lipid to be dispersed into the extracellular portions of the arterial wall. Thus, lipid may accumulate both intracellularly and extracellularly and may act as a local cause of injury.

When weighing the evidence linking tobacco usage with the development of atherosclerotic lesions, one should consider these theories of atherogenesis as well as the natural history of atherosclerosis presented earlier in order to make judgments about possible mechanisms and the stages at which the process might be affected.

Epidemiological Evidence Linking Cigarette Smoking With Atherosclerosis

Cigarette smoking is a major risk factor for coronary heart disease, peripheral vascular disease, and other clinically significant sequelae of atherosclerosis. A key question is whether cigarette smoking has an effect on the development of the arterial lesions, the terminal occlusive events, or both. Until the recent past, few investigators specifically designed studies to answer questions dealing with the association between cigarette smoking habits and the development of atherosclerotic lesions in the aorta and coronary arteries.

In the 1971 Report of the Surgeon General *The Health Consequences of Smoking* (*80*), reports of such studies were reviewed and summarized. Since that time, a number of additional reports have been published dealing with the relationship between cigarette smoking and atherosclerosis of the coronary arteries, aorta and

peripheral arteries, arterioles within the myocardium, and cerebral vessels. The evidence relating cigarette smoking and autopsy evidence of atherosclerotic disease in each of these areas is reviewed separately and summarized in individual tables in this section.

Coronary Arteries

Table 1 summarizes the studies that have examined the relationship between cigarette smoking and autopsy evidence of atherosclerosis in the coronary arteries. Auerbach et al. (*6*) found more coronary atherosclerosis in smokers than in nonsmokers and a concomitant increase in the amount of atherosclerosis with the amount of cigarette smoking. An interim report by Strong et al. (*75*) concluded that atherosclerotic involvement of aortas and coronary arteries was greatest in heavy smokers and least in nonsmokers among autopsied men in New Orleans. A report by Viel et al. (*81*) on accidental deaths in Chile stated that there was no relationship between atherosclerotic lesions and the use of tobacco; however, examination of the data indicated that heavy smokers in the 50- to 54-year and 55- to 59-year age groups exhibited higher percentages of the left anterior descending coronary intima involved by atherosclerotic lesions than did nonsmokers. Apparently these differences were not statistically significant.

A detailed study of smoking and atherosclerosis in deceased men in New Orleans has been conducted. Several reports based on the findings of that study, as well as various interpretations of those findings, have been published. Strong and Richards (*74*) reported the basic findings on the association of cigarette smoking and atherosclerosis in 1,320 autopsied men in New Orleans, 25 to 64 years of age. Coronary lesions were evaluated visually in coded specimens and objectively by analysis of post mortem radiographs. Using schedules that had been tested on pairs of living persons (*45*), interviewers obtained estimates of cigarette smoking habits of the deceased men from surviving relatives. Data were compared for black men and white men and also were analyzed in groups according to the presence or absence of diseases thought to be associated with smoking or with coronary heart disease (emphysema, lung cancer, myocardial infarction, hypertension, diabetes mellitus, stroke, etc.). Atherosclerotic involvement of the coronary arteries was greatest in heavy smokers and least in nonsmokers for both races in the total sample and in the basal group (those cases least influenced by the bias of autopsy selection). The data for these groups are presented in Table 1.

The study by Strong and Richards (*74*) included approximately the same number of autopsied subjects from New Orleans as had the previously reviewed study by Auerbach et al. (*6*) in East Orange, New Jersey. Even though the methods of evaluation of arterial

TABLE 1.—Autopsy studies of atherosclerosis involving the coronary arteries

Study	Population	Data collection method	Measure of atherosclerosis	Results				
				Smoking	No atherosclerosis	Slight	Moderate	Advanced
Auerbach et al. (6)	1,372 autopsies of men who did not die of CHD	Interview with relatives	Visual protocol	None	5.6	57.3	21.8	15.3
				<20	2.6	30.9	37.3	29.2
				20–34	.8	19.7	42.1	37.4
				40+	.6	18.1	35.4	45.9
Avtandilov (8)	259 males and 141 female autopsies	Not specified	Not specified	Comparative size of mean area of atherosclerotic lesions in inner coat of coronary arteries				
					Right coronary artery		Left coronary artery	
					Smoker	Nonsmoker	Smoker	Nonsmokers
				30–39	15.5 (30)[1]	1.3 (32)	6.3[1]	2.2
				40–49	23.6 (34)	11.5 (27)	15.8[1]	4.4
				50–59	36.3 (39)[1]	14.8 (39)	27.9[1]	9.9
				60–69	31.9 (32)[1]	23.8 (36)	26.5[1]	22.5
				70–79	41.9 (18)	31.7 (36)	26.1	35.8
				NOTE: The results concerning aortic atherosclerosis are given in form of figure presentation of ridit-analysis.				
Viel et al. (81)	1,150 males and 290 females autopsied following violent death	Interview with relatives	Not specified	Graphic data presentation only, but no association noted				

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results
Strong et al. (75)	747 New Orleans males 20–64 years of age at death	Interviews with next of kin within 8 weeks of death	IAP protocol, visual grading, and optical scanning	
Strong and Richards (74)	1,320 autopsies of males aged 25–64	Interview with next of kin	Visual grading and optical scanning	Mean percent of coronary artery intimal surface involved with raised lesions for total sample, males

	Average number cigarettes smoked per day		
Age	0	1–24	25+
		White males	
25–34	3	8	10
35–44	21	27	26
45–54	32	37	39
55–64	36	45	47
		Black males	
25–34	4	4	12
35–44	12	16	23
45–54	19	31	35
55–64	32	31	33

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results
Auerbach et al. (4)	1,056 autopsies of male veterans	Interview with relatives	Visual and microscopic evaluation	Distribution (in percentages) of degrees of fibrous thickening, of atheroma, and of calcification by smoking habits standardized for age (microscopic coronary study)

Degree of findings	Never smoked regularly	Current cigarette smokers: <pack per day	1–2 packs per day	2+ packs per day	Cigar/ pipe	Ex-cigarette smokers
Fibrous thickening						
None	50.1	3.9	0.6	0.4	4.5	5.0
Slight	20.1	26.5	8.0	5.1	24.4	30.6
Moderate	29.0	59.1	72.6	72.3	54.8	57.4
Advanced	0.8	10.5	18.8	22.2	16.3	7.0
Atheroma						
None	82.5	74.5	69.9	66.1	68.2	72.8
Slight	4.1	4.0	3.7	3.1	4.5	3.9
Moderate	13.1	19.2	20.6	20.8	23.4	21.5
Advanced	0.3	2.3	5.8	10.0	3.9	1.8
Calcification						
None	85.8	81.5	78.1	73.5	75.5	79.2
Slight	4.5	4.1	3.8	4.3	6.2	4.3
Moderate	8.4	10.3	11.1	11.2	13.4	12.7
Advanced	1.3	4.1	7.0	11.0	4.9	3.8